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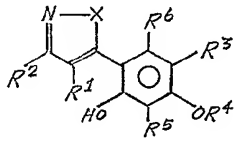
(19)

(54) PHARMACEUTICAL PREPARATIONS COMPRISING SUBSTITUTED RESORCINOLS

(71) We, CHEM. PHARMAZ. FABRIK DR. HERMANN THIEMANN G.M.B.H., a Body Corporate organized according to the laws of Germany, of Postfach 2069, 4628 Lünen/Westf., Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to pharmaceutical preparations comprising substituted resorcinols.

This invention provides a pharmaceutical preparation which comprises a resorcinol of the general formula I

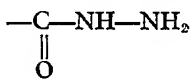


wherein

X represents an oxygen atom or an —NH group,

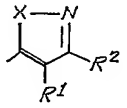
R^1 represents a hydrogen atom or a methyl group,

R^2 represents a hydrogen atom or a methyl, alkoxycarbonyl or



group,

R^3 represents the group



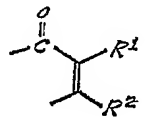
wherein R^1 and R^2 have the above-mentioned meaning,

R^4 represents a hydrogen atom,

R^5 represents a hydrogen atom or the group R^3,

R^6 represents a hydrogen atom or a hydroxyl group or

R^3 and R^4 together denote the radical



wherein R^1 and R^2 have the above-mentioned meaning, or a physiologically tolerable salt thereof in unit dosage form.

In a resorcinol of formula I, an alkyl group is preferably a lower alkyl group that is to say, an alkyl group having from 1 to 6 carbon atoms.

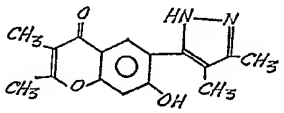
The invention also provides a pharmaceutical preparation which comprises a resorcinol of the general formula I as defined above or a physiologically tolerable salt thereof in admixture or conjunction with a pharmaceutically suitable carrier.

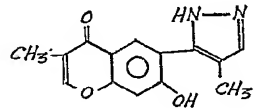
The preparations of the invention may be in a form suitable for oral administration; for example, pills, tablets, dragées and elixirs, or in a form suitable for administration by injection. The preparations may be formulated in the usual way, the carriers being, for example, corn starch, lactose, microcellulose, polyglycol 300 or polypropylene glycol. To manufacture an injectable solution using a resorcinol of the general formula I, it is advantageous to partially dissolve the compound in a solubilising agent, for example, propylene glycol or polyethylene glycol and then to adjust the pH of the mixture to pH 8 to 9 using a physiologically tolerable amine, for example, an alkanolamine, whereupon the remainder of the compound passes into solution, which is then brought to isotonicity. As the salts of the resorcinols of general formula I are more soluble than the resorcinols themselves, the above dissolution procedure is not generally necessary.

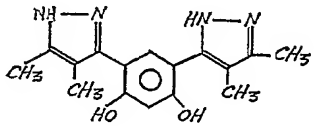
The preparations are preferably in unit dosage form, the unit dose of the resorcinol or salt thereof in oral preparations being from 50 to 500 mg, preferably 100 mg, and in injectable preparations from 10 to 100 mg, preferably 10 mg.

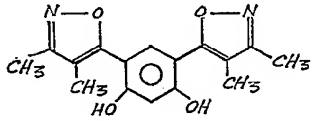
The preparations of the invention may be administered in daily doses of 3×100 mg orally or up to 3×10 mg by injection.

The resorcinols of general formula I preferred for use in the preparations of the invention are the following:



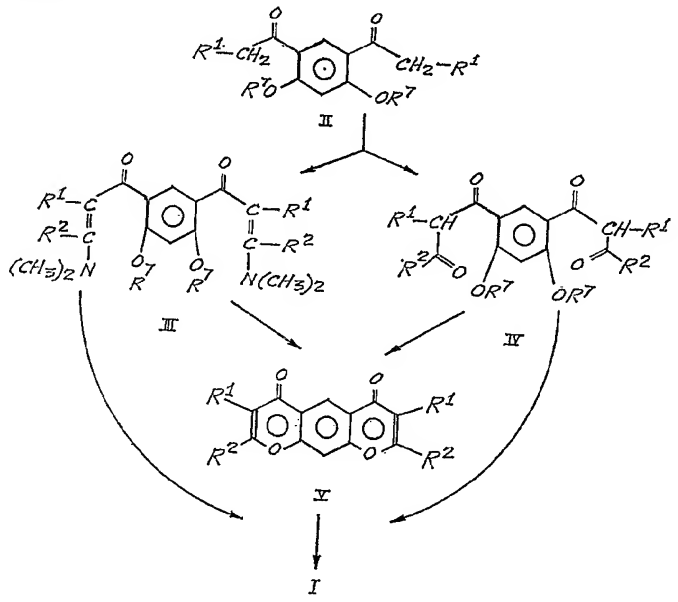






The resorcinols of general formula I and their salts possess valuable psychopharmacological, antiphlogistic, chemotherapeutic and immunosuppressive properties as well as an action on the heart and circulation. Some of the compounds are also suitable for use as intermediate products for the manufacture of other pharmacologically active compounds.

A resorcinol of the general formula I may be obtained according to the following reaction scheme:



R^1 and R^2 have the meanings given above and
R^7 represents a hydrogen atom or a $-CH_3$ or $-CH_2-O-CH_3$ group.

A substituted acetophenone derivative II can be reacted with an amide-acetal, or by ester condensation, to give a compound of formula III or IV, respectively, which compound then reacts either directly or after conversion to a compound of formula V, by warming with hydrazine or hydroxylamine, to give a compound of the general formula I.

Examples of the manufacture of resorcinols of the general formula I:

Example 1

Stage A:

4,6-Diacetyl-resorcyl-di(methoxymethyl ether)

23.8 g of the sodium salt of 4,6-diacetylresorcinol in 250 ml of dry tetrahydrofurane are stirred overnight with 17.7 g of chlorodimethyl ether at room temperature. 2 N sodium hydroxide solution is then added and the two phases are separated. The aqueous phase is extracted with chloroform. The combined organic phases are evaporated and the product is recrystallised.

Yield: 70% of theory
Colourless crystals, melting point=74°C (ethanol)
Analysis:

Calculated: C, 59.56%; H, 6.38%
Found: C, 59.03%; H, 6.53%

Stage B:

4,6-Di(ω-formylacetyl)-resorcyl-di-(methoxymethyl ether)

28.2 g of 4,6 - diacetyl - resorcyl - di(methoxymethyl ether) and 37.04 g of formic acid ethyl ester are dissolved in absolute ether and stirred with 35.1 g of dry potassium methylate for 16 hours at room temperature. The red salt is then filtered off and immediately hydrolysed with 0.3 N acetic acid. The crystals are rapidly filtered off, being of low stability.

Yield: 50% of theory.
Light yellow crystals, melting point=111°C (isopropanol)
IR: 3,000, 2,900 and 1,600/cm
NMR ($CHCl_3$): 3.5 (s, 6H), 5.33 (s, 4H) 6.36 (d, 2H, J=5Hz), 7.0 (s, 1H), 8.23 (d, 2H, J=5Hz), 8.5 (s, 1H)

Stage C:

Benzo(1,2-b:5,4-b')-bi-4-pyrone

33.8 g of 4,6 - di(ω - formylacetyl) - resorcyl - di(methoxymethyl ether) in 100 ml of 3 N sulphuric acid are heated to 100°C.

Yield: 30% of theory.
Colourless crystals, melting point=325°C (acetic acid)
Analysis:

Calculated: C, 67.30%; H, 2.82%
Found: C, 67.05%; H, 2.80%

Stage D:

4,6-Di(pyrazolo-3)-resorcinol

21.4 g of benzo(1,2 - b:5,4 - b') - bi - 4 - pyrone are dissolved in 300 ml of hot alcohol and boiled with 35.8 g of 80% strength aqueous hydrazine hydrate solution for 2 hours under reflux. After cooling—and if necessary, concentrating the solution—the crystals which have precipitated are filtered off.

Yield: 85% of theory.
Colourless crystals, melting point=269°C (ethanol)
Analysis:

Calculated: C, 59.50%; H, 4.16%; N, 23.13%
Found: C, 59.33%; H, 4.36%; N, 23.10%

Example 2

4,6-Di(5-isoxazolo)-resorcinol

5.3 g of benzo(1,2, - b:5,4 - b') - bi - 4 - pyrone, 4.2 g of hydroxylamine hydrochloride and 5.9 g of potassium acetate in 100 ml of glacial acetic acid are boiled for 2 hours under reflux. After concentrating the mixture, water is added and the product is filtered off.

Yield: 60% of theory.
Colourless crystals, melting point=360°C (DMFA/H_2O)
UV_{max}: 322 and 262 nm (dioxane)
Analysis:

Calculated: C, 59.02%; H, 3.30%; N, 11.47%
Found: C, 59.15%; H, 3.70%; N, 11.28%

Example 3

2,3-Dimethyl-6-(4,5-dimethylpyrazole-3)-7-hydroxy-chromone

27.0 g of $\alpha,\alpha',\beta,\beta'$ - tetramethyl - [benzo -]16,3,4di(γ - pyrone)] (manufactured according to Wittig, Ber. dtsch. chem. Ges. 59, 116 (1926)) dissolved in boiling ethanol and boiled with 35.8 g of 80% strength aqueous hydrazine hydrate solution for 2 hours under reflux.

The solution is allowed to cool and is concentrated if necessary and the crystals which have precipitated are filtered off.

Yield: 75% of theory.
Colourless crystals, melting point=360°C (DMF)
UV_{max}: 328, 316 and 273 nm (dioxane)
Analysis:

Calculated: C, 67.58%; H, 5.67%; N, 9.85%
Found: C, 67.92%; H, 5.53%; N, 9.77%

Example 4

Stage A:

3,7-Dimethyl-benzo(1,2-b:5,4-b')-bi-4-pyrone

22.2 g of 4,6 - dipropionylresorcinol and 26.2 g of N,N-dimethylformamide-dimethylacetal are heated under reflux in boiling absolute xylene for 2 hours. At the same time, the methanol produced is distilled off. After cooling, the precipitate is filtered off and recrystallised.

The cyclisation to give the 4-pyrone is carried out by stirring in 3 N sulphuric acid at 100°C for one hour.

Yield: 75% of theory.
Colourless crystals, melting point=224°C (acetic acid)
Analysis:

Calculated: C, 69.42%; H, 4.16%
Found: C, 67.26%; H, 4.33%

Stage B:

3-Methyl-6-(4-methylpyrazole-3)-7-hydroxy-chromone

24.2 g of 3,7 - dimethylbenzp(1,2 - b:5,4 - b') - bi - 4 - pyrone are dissolved in boiling ethanol and heated with 35.8 g of 80% strength aqueous hydrazine hydrate solution for 2 hours under reflux. The solution is allowed to cool and is concentrated if necessary and the crystals which have precipitated are filtered off.

Yield: 60% of theory.
Colourless crystals, melting point=272°C (ethanol)
Analysis:

Calculated: C, 65.61%; H, 4.72%; N, 10.93%
Found: C, 64.55%; H, 5.16%; N, 10.07%

Example 5

4,6-Di(4,5-dimethylpyrazole-3-)resorcinol

5 g of $\alpha,\alpha',\beta,\beta'$, - tetramethyl - [benzo - 1.6,3.4 - di(γ - pyrone)] in 50 ml of 80% strength aqueous hydrazine hydrate are stirred for 2 hours at 110°C bath temperature.

Water is then added and the mixture is slightly acidified with acetic acid. Crystals separate out, and are filtered off.

Yield: 70% of theory.
Colourless crystals, melting point=302°C (ethanol)
UV_{max}: 310, 285, 257 and 249 nm (dioxane)
Analysis:

Calculated: C, 64.41%; H, 6.08%; N, 18.78%
Found: C, 64.62%; H, 6.11%; N, 18.81%

Example 6

4,6-Di(4-methylpyrazole-3)-resorcinol

5 g of 3,7 - dimethyl - benzo(1,2, - b:5,4 - b') - bi - 4 - pyrone in 50 ml of 80% strength aqueous hydrazine hydrate are stirred for 2 hours at 110°C bath temperature.

Water is then added and the mixture is slightly acidified with acetic acid. Crystals separate out, and are filtered off.

Yield: 70% of theory.
Colourless crystals, melting point=283°C (ethanol)
Analysis:

Calculated: C, 62.21%; H, 5.22%; N, 20.73%
Found: C, 62.34%; H, 5.18%; N, 20.65%

Example 7

Stage A:

4,6-Di(1,3-propanedione-3-carboxylic acid ethyl ester)-resorcyl-di(methoxymethyl ether)

28.2 g of 4,6 - diacetyl - resorcyl - di(methoxymethyl ether) and 73.8 g of oxalic acid diethyl ester are dissolved in absolute ether and stirred with 35.1 g of dried potassium methylate for 16 hours at room temperature. The red salt is then filtered off and immediately hydrolysed with 0.3 N acetic acid. The crystals are rapidly filtered off; their stability is low.

Yield: 75% of theory.
Yellow needles, melting point=135°C (ethanol)
IR: 3,000, 2,900, 1,740 and 1,600/cm
Analysis:

Calculated: C, 54.77%; H, 5.43%
Found: C, 55.50%; H, 5.22%

Stage B:

4,6-Di(5-carboxylic acid ethyl ester-pyrazole-3)-resorcinol

48.2 g of 4,6 - di(1,3 - propanedione - 3 - carboxylic acid ethyl ester) - resorcyl - di(methoxymethyl ether) are dissolved in boiling ethanol and boiled with 35.8 g of aqueous 80% strength hydrazine hydrate solution for 2 hours under reflux. After cooling, the crystals are filtered off and briefly warmed in a mixture of 0.3 N HCl, water and ethanol (1:1:1), allowed to cool and again filtered off.

Yield: 70% of theory.
Colourless crystals, melting point=249°C (DMFA/H_2O)
UV_{max}: 314 and 240 (dioxane)
Analysis:

Calculated: C, 56.25%; H, 4.20%; N, 14.58%
Found: C, 53.99%; H, 4.92%; N, 14.13%

Example 8

Stage A:

2-Carboethoxy-6-acetyl-7-hydroxy-chromone

6.9 g of sodium are dissolved in 100 ml of absolute alcohol in a three-necked flask equipped with a stirred and reflux condenser. A solution of 9.7 g of diacetyl-resorcinol and 8.0 g of oxalic acid diethyl ester in 150 ml of boiling alcohol is added thereto. After stirring for one hour at the boil, the product is filtered off, hydrolysed with 100 ml of 3 N sulphuric acid and then cyclised in alcohol by means of sulphuric acid, by heating for two hours.

Yield: 70% of theory.
Colourless crystals, melting point=158°C (ethanol)
Analysis:

Calculated: C, 60.87%; H, 4.38%
Found: C, 59.96%; H, 4.45%

Stage B:

2,8-Dicarboethoxy-benzo(1,2-b:5,4-b')-bi-4-pyrone

13.8 g of sodium are dissolved in 100 ml of absolute alcohol in a three-necked flask with a stirrer and reflux condenser. A solution of 27.6 g of 2 - carboethoxy - 6 - acetyl - 7 - hydroxy - chromone and 16.1 g of oxalic acid diethyl ester in 150 ml of alcohol is added thereto. After stirring for one hour at the boil, the product is filtered off, hydrolysed with 100 ml of 3 N sulphuric acid and then cyclised in alcohol with sulphuric acid by heating for two hours.

Yield: 50% of theory.
Colourless crystals, melting point=233°C (ethanol)
Analysis:

Calculated: C, 60.34%; H, 3.94%
Found: C, 59.37%; H, 4.13%

Stage C:

4-(5-Carboxylic acid ethyl ester-pyrazole-3)-6-(5-carboxylic acid hydrazide-pyrazole-3)-resorcinol

35.8 g of 2,8 - dicarboethoxy - benzo(1,2 - b:5,4 - b') - bi - 4 - pyrone are dissolved in boiling ethanol and heated for 2 hours under reflux with 35.8 g of 80% strength aqueous hydrazine hydrate solution. The solution is allowed to cool and is concentrated if necessary, and the crystals which have precipitated are filtered off.

Yield: 50% of theory.
Colourless needles, melting point=290°C (ethanol/water)
UV_{max}: 316 and 240 nm (dioxane)
Analysis:

Calculated: C, 51.61%; H, 4.06%; N, 22.57%
Found: C, 49.76%; H, 4.52%; N, 21.02%

Example 9

2,3-Dimethyl-6(3,4-dimethyl-isoxazole-5)-7-hydroxychromone

6.76 g of $\alpha_2\alpha',\beta_2\beta'$ - tetramethyl - [benzo - 1.6,3.4 - di(γ - pyrone)], 4.2 g of hydroxylamine hydrochloride and 5.9 g of potassium acetate in 100 ml of glacial acetic acid are boiled for 2 hours under reflux.

After concentration, water is added and the product is filtered off.

Yield: 50% of theory.
Colourless flakes, melting point=307°C (ethanol)
UV_{max}: 310 and 250 nm (dioxane)
Analysis:

Calculated: C, 67.36%; H, 5.30%; N, 4.91%
Found: C, 67.44%; H, 5.23%; N, 4.90%

Example 10

3-Methyl-6(4-methylisoxazole-5)-7-hydroxy-chromone

6.1 g of 3,7 - dimethyl - benzo(1,2 - b: 5,4 - b') - 4 - pyrone, 4.2 g of hydroxylamine hydrochloride and 5.9 g of potassium acetate in 100 ml of glacial acetic acid are boiled for 2 hours under reflux. After concentration, water is added and the product is filtered off.

Yield: 50% of theory.
Colourless needles, melting point=266°C (ethanol)
Analysis:

Calculated: C, 65.37%; H, 4.31%; N, 5.44%
Found: C, 64.98%; H, 4.41%; N, 5.43%

Example 11

4,6-Di(3,4-dimethyl-isoxazole-5)-resorcinol

27.03 g of $\alpha_2\alpha',\beta_2\beta'$ - tetramethyl - [benzo - 1.6,3.4 - di(γ - pyrone)] and 10.5 g of an approx. 70% strength ethanolic hydroxylamine solution are stirred for 2 hours at 100°C bath temperature. After cooling, water is added.

Yield: 50% of theory.
Colourless crystals, melting point=297°C (ethanol)
Analysis:

Calculated: C, 63.99%; H, 5.37%; N, 9.33%
Found: C, 63.86%; H, 5.47%; N, 9.31%

Example 12

1,3,5-Tri(pyrazole-3)-2,4,6-trihydroxy-benzene

5.0 g of benzo(1,2, - b: 3,4 - b': 5,6 - b'') - tri - 4 - pyrone are dissolved in 100 ml of 80 strength aqueous hydrazine hydrate and the solution is stirred for 1 hour at 100°C 3 N acetic acid is then added and the precipitate is reprecipitated from glacial acetic acid/water or 0.1 N sodium hydroxide solution.

Yield: 50% of theory.
Light yellow crystals, melting point=360°C
UV_{max}: 306 nm (acetic acid)
Analysis:

Calculated: C, 55.56%; H, 3.73%; N, 24.91%
Found: C, 52.20%; H, 3.80%; N, 23.4 %

Example 13

4,6-Di(ω-nitrilo-acetyl)-resorcinol

4,6 - Di(5 - carboxylic acid ethyl ester - pyrazole - 3) - resorcinol are heated under reflux for 30 minutes with excess sodium alcoholate in ethanol. After concentration and acidification, the product is filtered off.

Yield: 40% of theory.
Yellow crystals, melting point=>360°C (ethanol)
IR: 2,950, 2,200 and 1,630/cm
Analysis:

Calculated: C, 59.02%; H, 3.30%; N, 11.47%
Found: C, 58.00%; H, 2.88%; N, 12.33%

Example 14

2,8-Di(N-hydroxyethyl carboxylic acid amide)-benzo(1,2-b:5.4-b')-bi-4-pyrone

35.8 g of 2,8 dicarboethoxy - benzo(1,2 - b:5,4 - b') - bi - 4 - pyrone are dissolved in boiling ethanol and heated with 13.4 g of 2-aminoethanol for 2 hours under reflux. The solution is allowed to cool and is concentrated if necessary and the crystals which have precipitated are filtered off.

Yield: 50% of theory.
Yellow crystals, melting point=226°C (ethanol)
UV_{max}: 379, 289 and 258 nm (dioxane)
Analysis:

Calculated:	C, 55.67%;	H, 4.15%;	N, 7.21%
Found:	C, 50.10%;	H, 4.90%;	N, 8.10%

The following Examples illustrate the invention:

Example 15

The compound of Example 11 is ground to give a fine powder of particle size 20—50μ. The powder is then mixed with lactose and micro-cellulose and is granulated with a gelatine solution. The granules, with addition of the carriers listed below are pressed to give tablets. Dragées are produced by pressing the mixture of granules and auxiliaries to produce cores and dragée-coating the cores in the usual manner.

The tablets and dragée cores have the following composition:

4,6-Di-(3,4-dimethyl-isoxazole-5)-resorcinol	100 mg
Micro-cellulose	15 mg
Lactose	10 mg
Talc	5 mg
Gelatine	5 mg

Example 16

A capsule is produced by mixing finely powdered substance from Example 11 with lactose, granulating the mixture with isopropanol, mixing the granules with D-(+)-lactose and filling this mixture into hard gelatine capsules.

The finished mixture has the following composition:

4,6-Di-(3,4-dimethyl-isoxazole-5)-resorcinol	100 mg
Lactose	40 mg
D-(+)-lactose	15 mg

Example 17

An injectable solution is prepared by partially dissolving finely powdered active compound from Example 11 in propylene glycol or polyethylene glycol and adjusting the solution/suspension to pH 8—9 with a physiologically tolerable alkanolamine. On doing so, the remainder of the active compound dissolves. A ready-to-inject solution has the following composition:

4,6-Di-(3,4-dimethyl-isoxazole-5)-resorcinol	10 mg
Propylene glycol, 25% strength aqueous solution adjust to pH 8.5—9 with approx. 10% strength aqueous diethanolamine solution	4 ml
Make up with distilled water to	5 ml

The pharmacological tests mentioned below were carried out according to standard methods such as are described by R. A. Turner in "Screening Methods in Pharmacology, Volumes 1 and 2, Academic Press, New York, 1965 and 1971".

The LD_{50} of the substances tested below is greater than 500 mg/kg in rats and mice, when administered orally.

1) Nicotine convulsion in mice:

The latency time of the clonic and tonic-clonic convulsions during an intravenous infusion of nicotine in mice was measured. The prior treatment with the test substances was carried out orally 1 hour before the experiment.

2) Spontaneous motility of mice:

The spontaneous motility was measured in treadmills, the measurement being carried out under constant light conditions. The motility was in each case measured for 1 hour. Because of the influence of the time of day, a control group of equal size was examined simultaneously with each test group.

3) Oxotremorin test in mice:

In this test, the central and peripheral, anticholinergic action of the test substances is examined. The typical choline-mimetic symptoms caused by oxotremorin, for example, salivation, lacrimation, excretion of urine and faeces, and hypothermia served as a model. For quantitative assessment, the intensity and latency period of the tremor, and the effect on the rectal temperature, were employed in particular. The test substance had been administered orally 1 hour before the experiment.

4) Hexobarbital sleeping time in mice:

The influence of the sleep narcosis condition in mice, produced by hexobarbital, was determined by measuring the "sleeping time". The "sleeping time" is considered to have ended when the getting-up reflexes can again be triggered normally.

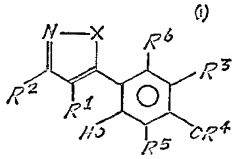
The results are summarised in the table which follows:

TABLE

Compound from Example	Inhibition of nicotine convulsion (200 mg/kg administered orally)	Hexobarbital sleeping time (200 mg/kg)	Inhibition of spontaneous mobility	Oxotremorin (200 mg/kg administered orally) Inhibition of tremor	Oxotremorin (200 mg/kg administered orally) Inhibition of rectal temperature
3	+79%		−35%	+71%	
4B		−12% (Antagonistic)		+21%	+90%
5	+137%	+22% (Synergistic)		+15%	−40%
11		+20% (Synergistic)			+43%

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation which comprises a resorcinol of the general formula I



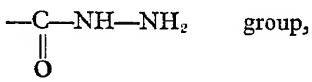
(I)

wherein

X represents an oxygen atom or an —NH group,

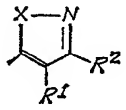
R^1 represents a hydrogen atom or a methyl group,

R^2 represents a hydrogen atom or a methyl, alkoxycarbonyl or



group,

R^3 represents the group



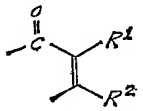
wherein R^1 and R^2 have the above-mentioned meaning,

R^4 represents a hydrogen atom,

R^5 represents a hydrogen atom or the group R^3,

R^6 represents a hydrogen atom or a hydroxyl group or

R^3 and R^4 together denote the radical



wherein R^1 and R^2 have the above-mentioned meaning, or a physiologically tolerable salt thereof in unit dosage form.

2. A pharmaceutical preparation which comprises a resorcinol as defined in claim 1 or a physiologically tolerable salt thereof in admixture or conjunction with a pharmaceutically suitable carrier.

3. A pharmaceutical preparation as claimed in claim 2, in unit dosage form.

4. A pharmaceutical preparation as claimed in any one of claims 1 to 3, in a form suitable for oral administration.

5. A pharmaceutical preparation as claimed in claim 4 and which is in unit dosage form, which comprises from 50 to 500 mg of the resorcinol or salt thereof per unit dose.

6. A pharmaceutical preparation as claimed in claim 5, which comprises 100 mg of the resorcinol or salt thereof per unit dose.

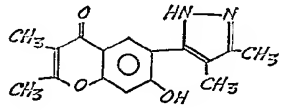
7. A pharmaceutical preparation as claimed in claim 2 or claim 3, in a form suitable for administration by injection.

8. A pharmaceutical preparation as claimed in claim 7, which also comprises a solubiliser.

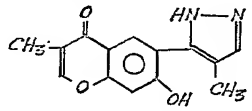
9. A pharmaceutical preparation as claimed in claim 7 or claim 8 and which is in unit dosage form, which comprises from 10 to 100 mg of the resorcinol or salt thereof per unit dose.

10. A pharmaceutical preparation as claimed in claim 9, which comprises 10 mg of the resorcinol or salt thereof per unit dose.

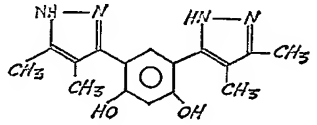
11. A pharmaceutical preparation as claimed in any one of claims 1 to 10, wherein the resorcinol has the formula



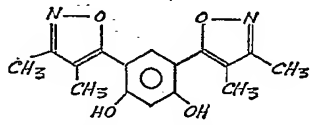
12. A pharmaceutical preparation as claimed in any one of claims 1 to 10, wherein the resorcinol has the formula



13. A pharmaceutical preparation as claimed in any one of claims 1 to 10, wherein the resorcinol has the formula



14. A pharmaceutical preparation as claimed in any one of claims 1 to 10, wherein the resorcinol has the formula



15. A pharmaceutical preparation as claimed in claim 2 and which is substantially as described in any one of Examples 15 to 17 herein.

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